

**Buprenorphine may be as Effective as Methadone  
as a Maintenance Treatment for Opiate Dependence**

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## Contents

|                        |    |
|------------------------|----|
| Executive Summary..... | i  |
| Introduction.....      | 1  |
| Methods and Data.....  | 2  |
| Results.....           | 5  |
| Discussion.....        | 11 |
| Acknowledgements.....  | 14 |
| References.....        | 15 |

## **Titles of Tables**

|          |  |    |
|----------|--|----|
| Table 1. | Randomized Clinical Trials Comparing Buprenorphine to Methadone For Opiate Dependence.....   | 3  |
| Table 2. | Patients' Mean Percent Positive Urinalysis for Illicit Opiates in Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence..... | 6  |
| Table 3. | Difference in Retention in Treatment in Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence.....                           | 8  |
| Table 4. | Ranking of Effect Size and Relative Treatment Dose in Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence.....             | 10 |



## Executive Summary

**Background.** The unique pharmacologic properties of buprenorphine may make it a useful maintenance therapy for opiate addiction. This meta-analysis considers the effectiveness of buprenorphine relative to methadone.

**Method.** Data from five randomized clinical trials comparing buprenorphine to methadone were analyzed. Retention in treatment was analyzed with a Cox proportional hazards regression. Urinalyses for opiates were studied with analysis of variance and a common method of handling missing values. A meta-analysis was used to combine these results.

**Results.** Patients who received buprenorphine had 1.26 times the relative risk of treatment failure (95% confidence interval of 1.01-1.57) and 8.3% more positive urinalyses (95% confidence interval of 2.7% to 14%) than patients receiving methadone. There was substantial variation in outcomes in the different trials.

**Conclusions.** The variation between trials may be due to differences in dose levels, patient exclusion criteria, and provision of psychosocial treatment. The difference in the effectiveness of buprenorphine and methadone may be statistically significant, but the differences are small compared to the wide variation in outcomes in different methadone treatment programs.

**Recommendations.** Further research is needed to determine if buprenorphine is more effective than methadone in particular settings or in particular subgroups of patients. In the interim, information on the relative efficacy of buprenorphine found from this analysis should be applied to economic models of its cost-effectiveness as a maintenance therapy.



## Introduction

There are some 750,000 heroin users in the United States (Spencer, 1989). While some individuals with opiate dependence disorders are successfully treated with naltrexone or in drug-free treatment programs, methadone maintenance is the only widespread treatment that has high rates of success in reducing intravenous use of heroin.

Despite the demonstrated efficacy of methadone, only 100,000 individuals are in U.S. methadone maintenance programs (U.S. SAMHSA, 1992). A number of factors have limited the use and effectiveness of this treatment. Federal, state, and local laws limit use; new methadone clinics have difficulty obtaining approval from local authorities (Cooper, 1989). Many treatment programs dispense methadone at inadequate doses (Ball and Ross, 1991; U.S. General Accounting Office, 1990). Some patients wish to avoid the social stigma associated with methadone. Others do not like the subjective effects of methadone or the structure of treatment, including daily clinic visits and periodic psychosocial interventions. Public funding is inadequate to provide treatment to all who desire it.

Buprenorphine has been proposed as a new therapy that could help those who are not already receiving treatment, stem the incidence of HIV and other diseases, and help alleviate other problems resulting from opiate abuse. It has several potential advantages. Since it is a partial agonist, there is a ceiling on its ability to cause respiratory depression; administration of buprenorphine is thus less likely to result in an overdose. Its use results in less physical dependence, so that it is easier to detoxify from buprenorphine than from methadone (Jasinski et al., 1978).

A combination of buprenorphine and the opiate antagonist naloxone has limited possibility for abuse. If the combination drug is administered by injection by an opiate dependent individual, the naloxone blocks the effect of the buprenorphine. This property suggests that it has a role as a take-home maintenance medication. A trial of the safety and effectiveness of this combination drug has been completed. A new trial will consider the use of the combination drug as a maintenance therapy prescribed in primary care practice.

As with any new health care technology, the adoption of buprenorphine will depend on its cost-effectiveness in comparison to the available alternatives. The health care payer will add buprenorphine to the formulary only if its benefits justify its cost. Information about the relative efficacy of buprenorphine and methadone will be useful for this decision. Although efficacy trials of buprenorphine as a maintenance therapy have lasted 6 months or less, there is a great deal of information about the long-term effectiveness of methadone therapy.

If the efficacy of buprenorphine can be calibrated in terms of the efficacy of methadone, the extensive information on the outcomes of methadone maintenance may be used to model the long-term consequences of buprenorphine treatment. Such information will help determine if health care sponsors will approve of buprenorphine as a maintenance therapy, and, if so, what price they should be willing to pay for it.

This report presents a meta-analysis of trials comparing the effectiveness of buprenorphine relative to methadone. The trials we studied, and the methods of the meta-analysis we employed, are described. This is followed by presentation of our results. The report ends with a discussion of the implication of these results and a description of areas where further study is needed.

### **Methods and Data**

We searched for all double-blind randomized clinical trials that compared methadone to buprenorphine. We found five published studies which tested buprenorphine in daily doses of at least 6 mg (Johnson et al., 1992; Kosten et al., 1993; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1994). We found a sixth trial that tested a lower, 2 mg dose of buprenorphine (Bickel et al., 1988). We did not include it in our study because this dose was too low to be comparable to the data from the other trials.

In each study, patients were randomly assigned to receive either methadone or buprenorphine. The characteristics of the five studies are presented in Table 1. Buprenorphine doses varied between 6 mg and 12 mg per day. Methadone doses varied from 50 to 80 mg per day. Although four of the studies included a group that received a lower dose of methadone, and two studies included a group receiving a lower dose of buprenorphine, we limited our analysis to the groups receiving the largest dose of each drug in each trial because these are the doses that are the most comparable across studies.

The studies followed patients for periods of 16 to 26 weeks. Two of the studies also followed patients during a subsequent 8 to 10 week long detoxification period, but we did not consider these detoxification periods in our analysis.

**Table 1. Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence**

| <b>Study</b>        | <b>Methadone dose (mg/day)</b> | <b>Buprenorphine dose (mg/day)</b> | <b>Study length (weeks)</b> | <b>Number of patients<sup>a</sup></b> |
|---------------------|--------------------------------|------------------------------------|-----------------------------|---------------------------------------|
| Johnson (1992)      | 60                             | 8                                  | 17 <sup>b</sup>             | 107                                   |
| Strain (1994)       | 50                             | 8                                  | 16 <sup>c</sup>             | 164                                   |
| Schottenfeld (1997) | 65                             | 12                                 | 24                          | 57                                    |
| Ling (1996)         | 80                             | 8                                  | 26                          | 150                                   |
| Kosten (1993)       | 65                             | 6                                  | 24                          | 62                                    |

a. Patients in these two treatment groups receiving the doses listed

b. Followed by 8 week detoxification period

c. Followed by 10 week detoxification period

Although a variety of outcomes were measured in these five trials, two measures were used in all studies. Every study conducted a periodic urinalysis for opiates and reported the length of time that each patient remained in treatment.

The goal of maintenance therapy is to reduce opiate use. This can be regarded as having three dimensions: (1) the percentage reduction in use that occurs while therapy is received, (2) the length of time that therapy continues, and (3) the effect of the therapy after it is discontinued. The urinalysis results represent a measure of this first dimension. Retention data is a measure of the second. Since no data was gathered on individuals who discontinued therapy, the third dimension was not measured. This benefit is likely to be negligible, however. Other studies have found that most individuals who drop-out during their first year of methadone maintenance return to opiate abuse (Bertschy, 1995).

In order to apply the same analytical methods to all data, we obtained the original urinalysis and retention data on the patients in each of the individual studies. All studies regularly screened patients' urine for illicit opiates for as long as the patient continued in the study. The testing schedule varied from a minimum of one test per week to a maximum of three. For each patient there was a series of dichotomous values indicating whether the test was positive for opiates.

We calculated the percentage of urinalyses that were positive for each patient and the mean of these percentages for the patients in each group. Our meta-analysis sought to characterize the difference between buprenorphine and methadone as the difference in the mean percent positive urinalyses for each treatment group while still retained in treatment.

We used two different methods of handling missing urinalyses. The first method treated missing tests as positive, thereby creating a complete data set. This assumes that a patient who missed providing a specimen had been using illicit opiates. Since we considered only the period while the patient was retained in treatment, the assumption was not applied to tests missed because patients had dropped out or had been terminated from the study. The second method ignored missing values. This approach is valid if the missing status of the specimen provides no information—if patients who had used illicit opiates were just as likely to fail to provide a urine specimen as those who had abstained.

The other outcome measure was the length of time the patient was retained in treatment. Since patients were followed only until the last day of each study, this outcome was censored by the length of follow-up. We analyzed these data with a Cox proportional hazards model. The regression used the number of days the patient was retained as the dependent variable, and a single independent variable, an indicator which took a value of 1 if the patient was in the buprenorphine treatment group. To provide a clear interpretation of the effect, we expressed the hazard parameter as the relative risk of treatment failure in buprenorphine compared to methadone.

For each study, we determined the difference in outcomes between the treatment groups. For the urinalysis data, we calculated the difference between the means of the buprenorphine and methadone treatment groups. For the retention data, we used the coefficient from the Cox proportional hazards regression.

We found the variance for these estimates for each study. For the urinalysis data, it was based on the standard deviation of the buprenorphine and methadone treatment groups, and the number of patients in each group. For the retention data, the variance was the square of the standard error of the Cox regression parameter.

We determined the weighted mean of the treatment effect differences found in the studies. The reciprocal of the variance was used to weight each study. We obtained the weighted mean over all studies, the variance of this estimate, and the 95% confidence interval around the mean difference.

We also tested the validity of the statistical assumptions needed to pool data for meta-analysis. This is a test of the homogeneity of the effect. The null hypothesis of this test is that the effect size is the same in all of the studies, that is, the studies are similar enough to be pooled. We used the Q statistic (a chi square) for the homogeneity of effects.

If the test was significant, then we reject the hypothesis of homogeneity, and conclude that the data from the different studies cannot be pooled. If this test was not significant (if we failed to reject the hypothesis of homogeneity), then we reported the weighted mean of the difference between the buprenorphine and methadone treatment groups.

## **Results**

The mean percent positive urinalyses provided by patients receiving buprenorphine, the mean percent positive provided by those receiving methadone, the difference in these means, and the confidence interval surrounding this difference, are presented in Table 2. This analysis treated missing values as if they were positive.

**Table 2. Patients' Mean Percent Positive Urinalysis for Illicit Opiates in Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence**

| Study   | Buprenorphine | Methadone | Difference               | Confidence Interval |   |        | Homogeneity Test (p value) |
|---|---------------|-----------|--------------------------|---------------------|---|--------|----------------------------|
| Johnson (1992)                                | 0.588         | 0.610     | -0.022                   | -0.142              | - | 0.097  |                            |
| Strain (1994)                                 | 0.547         | 0.497     | 0.051                    | -0.044              | - | 0.146  |                            |
| Schottenfeld (1997)                           | 0.544         | 0.389     | 0.155*                   | 0.001               | - | 0.310  |                            |
| Ling (1996)                                   | 0.542         | 0.372     | 0.169*                   | 0.066               | - | 0.273  |                            |
| Kosten (1993)                                 | 0.781         | 0.537     | 0.244*                   | 0.085               | - | 0.404  |                            |
| Summary based on 5 studies                    |               |           | (fails homogeneity test) |                     |   | 0.034* |                            |
| Summary based on 4 studies (excluding Kosten) |               |           | 0.083*                   | 0.027               | - | 0.140  | 0.074                      |

\* p < .05

The homogeneity test found that the effect of these five studies could not be considered homogeneous ( $\chi^2 = 10.4$ ,  $df = 4$ ,  $p = .033$ ), so it was not appropriate to report the mean difference in the effect based on all 5 studies. When we limited the analysis to the four studies that used at least 8 mg of buprenorphine, the homogeneity test was no longer significant (this excluded the trial reported by Kosten, which used a 6 mg dose). In these four studies patients receiving buprenorphine had an average of 8.3% more positive urinalyses than patients receiving methadone ( $z = 2.91$ ,  $p = .002$ ). The 95% confidence interval was 2.7% to 14%.

Adopting the assumption that missing values could be ignored had little effect on the result. Patients receiving buprenorphine had 8.0% more positive tests ( $z = 2.62$ ,  $p = .004$ ). The 95% confidence interval was 2.0% to 13.9%.

The effect of treatment on patient retention is presented in Table 3. Using all five studies, the test of homogeneity is not significant at the .05 level ( $\chi^2 = 8.1$ ,  $df = 4$ ,  $p = .088$ ). We calculated the mean difference in retention by combining the Cox regression parameters. Patients receiving buprenorphine had an average of 1.26 times the relative risk of treatment failure per unit of time than patients receiving methadone. The difference in risk was significant ( $z = 2.07$ ,  $p = .019$ ), with a 95% confidence interval of 1.01-1.57.

**Table 3. Difference in Retention in Treatment in Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence**

| <b>Study</b>                                  | <b>Relative<br/>Hazard<br/>Ratio</b> | <b>Confidence Interval</b> | <b>Homogeneity<br/>Test<br/>(p value)</b> |
|---|--------------------------------------|----------------------------|---|
| Johnson (1992)                                | 0.830                                | 0.515 - 1.339              |   |
| Strain (1994)                                 | 1.048                                | 0.679 - 1.617              |   |
| Schottenfeld (1997)                           | 1.343                                | 0.610 - 2.960              |   |
| Ling (1996)                                   | 1.534*                               | 1.057 - 2.226              |   |
| Kosten (1993)                                 | 2.437*                               | 1.208 - 4.917              |   |
| Summary based on 5 studies                    | 1.263*                               | 1.013 - 1.575              | 0.088                                     |
| Summary based on 4 studies (excluding Kosten) | 1.175                                | 0.931 - 1.483              | 0.224                                     |

\* p < .05

When the retention analysis was limited to the four studies that tested 8 mg or more of buprenorphine, the patients receiving buprenorphine had 1.17 times the risk of treatment failure. This value was not significantly different from one ( $z = 1.36$ ,  $p = .087$ ), with the 95% confidence interval ranging from 0.93 to 1.48.

The two outcome measures used by these trials are highly correlated. Table 4 presents a ranking of studies according to each outcome. Each study was ranked by the retention outcome, in the order of the lowest to highest relative hazard ratio between buprenorphine and methadone. The trial reported by Johnson is at the top of the ranking, as it was the study in which buprenorphine was the most effective at retaining patients. The trial reported by Kosten is at the bottom of the ranking because it showed buprenorphine to be the least effective.

Table 4 also presents the ranking of studies by urinalyses results. The trial reported by Johnson is again at the top of the ranking, as the urinalysis results in this study showed buprenorphine to be the most effective compared to methadone. The study reported by Kosten is again at the bottom of the ranking; the urinalysis data showed buprenorphine to be the least effective compared to methadone. The ranking of the five studies in terms of the relative effectiveness of buprenorphine is exactly the same for both outcomes.

**Table 4. Ranking of Effect Size and Relative Treatment Dose in Randomized Clinical Trials Comparing Buprenorphine to Methadone for Opiate Dependence**

| Study               | Rank of Effect of Buprenorphine<br>Relative to Methadone |            | Buprenorphine<br>Dose Divided<br>by Methadone<br>Dose | Rank of Relative<br>Dose of<br>Buprenorphine<br>Compared to<br>Methadone |
|---------------------|--|------------|---|--|
|                     | Retention  | Urinalyses |   |  |
| Johnson (1992)      | 1  | 1          | 0.13  | 3  |
| Strain (1994)       | 2  | 2          | 0.16  | 2  |
| Schottenfeld (1997) | 3  | 3          | 0.18  | 1  |
| Ling (1996)         | 4  | 4          | 0.10  | 4  |
| Kosten (1993)       | 5  | 5          | 0.09  | 5  |

## Comment

There was considerable heterogeneity of the effects found in the different trials. The homogeneity test found the urinalysis data from the five trials too dissimilar to be combined. If the tests of homogeneity were conducted with a critical p value of .10, then the retention data were also too dissimilar to be combined. When studies are heterogeneous, the statistical assumptions needed to pool the data and thereby draw conclusions from a meta-analysis are in doubt. The analyst must examine the sources of the heterogeneity. Differences in study design may be correlated with outcomes. We considered how these trials differed in the dose of drugs employed, in the types of patients enrolled, and in other methods used.

The studies employed different doses of both drugs. In order to combine these into a simple, one-dimensional measure, we divided the buprenorphine dose by the methadone dose (see Table 4). We also ranked the studies by this measure of relative dose of buprenorphine employed.

There was some correlation between the dose used and the outcomes in the study. The study with the lowest relative buprenorphine dose, the trial reported by Kosten, also found buprenorphine to have the lowest relative effectiveness. Ling's study used the next lowest relative dose and reported the second worst result. The starting doses employed in Strain's study were second in both the dose and outcomes rankings.

In the other two trials the relationship between dose and outcomes was not clear. The Schottenfeld study employed the highest relative dose of buprenorphine, but ranked third in its findings of the relative effectiveness of buprenorphine. The Johnson study used the third highest relative dose of buprenorphine and found the greatest relative effectiveness of buprenorphine. Factors other than the relative dose must explain the differences in the results found by Schottenfeld and Johnson.

One potential explanation may be the differences in patients enrolled. The Schottenfeld study included only those patients who were dependent on cocaine as well as opiates. Patients in the other studies reported lower levels of cocaine dependence; Ling's study excluded cocaine dependent patients altogether.

Three studies, those of Kosten, Ling, and Schottenfeld, excluded patients who were dependent on alcohol or sedatives. Buprenorphine performed the poorest in these three studies. The study reported by Strain included only those patients with little prior experience in methadone maintenance.

Different amounts of counseling were offered to the patients in the different studies. In the Johnson study counseling sessions were voluntary. At the other extreme, the Schottenfeld study required patients to attend group therapy and considered treatment to have failed if three consecutive sessions were missed.

The effectiveness of buprenorphine as a maintenance therapy will depend on several factors: the dose that is used, the types of patients treated, the treatment setting, and the formulation. Buprenorphine may be used at a higher dose than was given in these trials. In the three studies that found methadone to be significantly more effective than buprenorphine (Kosten et al., 1993; Ling et al., 1996; Schottenfeld et al., 1997), all three authors suggested that higher doses of buprenorphine may be needed. The most recent of these papers, which reported the results of the highest relative dose of buprenorphine, concluded with the comment that "daily doses even higher than 12 mg (of buprenorphine). . . may be required to achieve optimal results" (Schottenfeld et al., 1997). On the other hand, as a partial agonist, at higher doses, buprenorphine limits its own effect, and higher doses may actually reduce its effectiveness.

The adoption of buprenorphine may also depend on the patients who are treated. Buprenorphine may prove to be most effective in certain subgroups of patients (Resnick et al., 1991). The adoption of buprenorphine may also depend on the treatment setting. The study in which buprenorphine was more successful compared to methadone involved little psychosocial intervention (Johnson et al., 1992). This may suggest that there is an interaction between psychosocial treatments and maintenance drug, and that buprenorphine may have a role in a "medical maintenance" model of treatment.

A combination drug that includes buprenorphine and the narcotic antagonist naloxone is being tested as a possible take-home maintenance therapy. This could reduce some of the costs associated with maintenance therapy. Methadone treatment is more expensive because of the costs of complying with federal regulations. Additional cost is incurred by patients in making daily trips to a licensed clinic.

This meta-analysis determined that patients receiving a daily dose of between 8 and 12 mg of buprenorphine were 1.26 times more likely to drop out of treatment than patients receiving a 50 to 80 mg daily dose of methadone, and 8.3% more likely to have a positive urinalysis for opiates. Such differences must be placed in a clinical context.

Much larger differences in the dropout rates have been observed with different uses of methadone. For example, patients who received doses of less than 60 mg of methadone had nearly five times the risk of dropping out as those who received doses of 80 mg or more (Caglehorn and Bell, 1991). Patients who were not informed of their methadone dose were 3.17 times more likely to drop out than patients who were informed of their dose (Condelli and Duntelman, 1993).

Although we found a statistically significant difference in the effectiveness of buprenorphine and methadone, these differences do not appear to be of very great clinical significance. Methadone is not available to all opiate dependent individuals seeking treatment, and there are limited opportunities for expanding methadone treatment programs. This analysis of buprenorphine found it to be nearly as effective as methadone. Its adoption will depend on whether it is used to treat patients who do not

benefit from methadone.

Buprenorphine has the potential to reduce the harm caused by intravenous drug abuse. Health care decisionmakers will need to decide whether buprenorphine maintenance is worth adopting. They will need to consider the cost of this new maintenance therapy and its value in reducing the effects of opiate dependence, including HIV infection and high rates of mortality. This meta-analysis determined that buprenorphine is 92% as effective as methadone during treatment, and that treated patients are retained 85% as long. Decisionmakers will be assisted if these estimates are used to construct models of buprenorphine's cost-effectiveness.

Future trials will be needed to consider the effect of dose, treatment setting, drug formulation, and whether there are subgroups of patients who can best benefit from this treatment.

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